



Research Article

Hydrophilic Sugars for Enhancing Dissolution Rate of Cilostazol: Effect of Wet Co-Processing

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Abstract

Background: Cilostazol is an anti-platelets drug with considerable antithrombotic effects *in vivo*. Therefore, it is widely used by elderly patients. However, it suffers from poor bioavailability due to its low aqueous solubility. The objective of this work was to enhance the dissolution of cilostazol with the aim of formulating fast dissolving tablets for geriatrics and those of swallowing difficulties.

Methods: Ethanol-assisted co-grinding of cilostazol with sugar-based excipients was adopted. Sucralose and mannitol were used for this purpose as hydrophilic excipient as well as taste improving agents. The obtained products were investigated regarding differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction, scanning electron microscope (SEM) and *in vitro* drug dissolution. Fast disintegrating tablets were prepared and evaluated.

Results: Thermal behavior of the developed products reflected reduced crystallinity, it also suggested possible existence of new crystalline species with sucralose. Eutexia was also suggested for mannitol mixtures, that was supported by X-ray diffraction data. SEM indicated size reduction with the deposition of the drug as submicron particles over the excipient surface. Co-processing markedly improved cilostazol dissolution compared to unprocessed drug. The optimized formulations were successively formulated into fast disintegrating tablets.

Conclusion: This investigation introduced the wet grinding strategy with sugar excipients as a platform for the formulation of easy to use tablets with optimum drug release.

Introduction

Cilostazol is an inhibitor of phosphodiesterase III and suppresses Cyclic adenosine monophosphate (cAMP) degradation. This can increase the level of cAMP in platelets and blood vessels which results in vasodilatation and reduced platelet aggregation.¹ Consequently, cilostazol is used in the management of ischemic symptoms resulting from peripheral arterial occlusive diseases.² Cilostazol is a poorly and slowly soluble drug.³ In addition, cilostazol is a weak basic compound (pK_a 11.8), suggesting high degree of ionization throughout intestine.⁴ These factors contribute to the low and variable oral bioavailability of cilostazol. Enhancing the dissolution rate of this drug can provide a promising platform for enhanced bioavailability after oral administration.

Researchers employed different techniques to solve the problems contributing to reduced oral bioavailability of cilostazol. Size reduction employing spray drying or supercritical fluid techniques were investigated with good results.^{2,5} Others used inclusion complexation with

cyclodextrins with improved cilostazol bioavailability.¹ Authors went further to develop sulfonate and mesylate salts of cilostazol. These salts liberated cilostazol at a faster rate than the free base with fast liberation being manifested as better bioavailability relative to the unprocessed base of the drug.⁴

Simple co-processing with hydrophilic excipients has emerged as a promising strategy for enhanced dissolution rate of hydrophobic drugs. Sucralose, which is used as an artificial sweetener, was able to enhance the dissolution rate of various hydrophobic drugs like nateglinide and bicalutamide after co-processing.^{6,7} Xylitol was also employed to enhance the dissolution rate of felodipine.⁸ Mannitol is another hydrophilic sugar showed promising efficacy in enhancing the dissolution rate of olanzapine and etoricoxib after solid dispersion formation and as co-crystal conformer for hydrochlorothiazide.⁹⁻¹¹ Hydrophilic polymers have been extensively employed to fabricate solid dispersion with hydrophobic drugs with the goal of

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enhancing their dissolution pattern.^{12,13}

The main target of this research was to formulate cilostazol fast disintegrating tablets with subsequent enhanced dissolution rate. These tablets have received ever-increasing demand during the last decade. Therefore, the dissolution rate of cilostazol was first improved utilizing co-processing technique with hydrophilic sugars. Sucralose and mannitol were selected for this purpose. These excipients have a dual effect of being dissolution rate enhancers with sweet taste and good compressibility. Additionally, sucralose is an artificial sweetener that is not broken down by the body. Therefore, it is not caloric and can be used to prepare fast disintegrating tablets for diabetic patients.

Materials and Methods

Materials

Cilostazol was obtained as a gift sample from Delta Grand Pharma, Cairo, Egypt. Sucralose, mannitol, croscarmellose sodium, cross-povidone, magnesium stearate and Avicel PH102 were donated by Sigma for Pharmaceutical Industries, Quesna, Egypt. Sodium lauryl sulphate and ethanol (analytical grade) were purchased from El Nasr Chemical Company, Cairo, Egypt.

Method of preparation

Ethanol assisted co-grinding was used to prepare various mixtures of cilostazol with increasing molar ratio of sucralose or mannitol. The compositions of the prepared formulations are presented in Table 1. The adopted processing technique was similar to the previously reported method with slight modification.^{6,8} Cilostazol was mixed with the calculated amount of sucralose or mannitol and ethanol was added gradually with grinding to form smooth paste using mortar and pestle. This paste was subjected to continuous grinding for 30 minutes to form a dry powder. The process was repeated 4 times at the end of which the dry product was left to dry overnight. These formulations were kept in air-tight bottles till used. Pure cilostazol was subjected to the same procedure and

was taken as positive control. Additionally, mannitol and sucralose were individually subjected to the same process for interpretation of the physical state characterization data.

Assay of Cilostazol

This was accomplished using UV spectroscopy which employed UV-visible spectrophotometer (JENWAY, Staffordshire, UK). Stock solution containing 1mg/ml of the cilostazol was prepared in ethanol. Serial dilutions were prepared using 0.3% w/v sodium lauryl sulphate in water to prepare a series of concentrations in the range of 5 to 25 µg/ml. The absorbance values were recorded at 257 nm. The recorded absorbance values were plotted as a function of cilostazol concentration to construct the standard calibration graph showing linearity (R^2 value of 0.9937) in the tested range ($y = 0.041 \pm (0.00327) x - 0.0297 \pm (0.01208)$), where y and x refer to absorbance and concentration, respectively).

Solid state characterization of the prepared formulations Fourier transform infrared spectroscopy (FTIR)

The potential interactions between cilostazol and tested sugars were monitored using FTIR (Bruker Tensor 27 FTIR spectrophotometer, Ettlingen, Germany). The test was performed for drug and excipients before and after processing or co-processing. The samples were blended with potassium bromide and were compressed into thin disks before loading onto the sample holder and scanning from 4000 to 400 cm^{-1} . Data collection was conducted under potassium bromide diffuse reflectance mode using a DLATGS detector. The collected data were analyzed using Opus IR, software.

Differential scanning calorimetry (DSC)

The thermal behavior of samples was monitored before and after processing using Perkin Elmer DSC6 (Waltham, MA, USA). Prior to use, the DSC equipment was calibrated for temperature and heat capacity using zinc and indium. The drug or its equivalent (2-4 mg) was loaded into aluminum

Table 1. The compositions of the co-processed drug with either sucralose (CS) or Mannitol (CM) presented as both molar and weight ratios, together with dissolution parameters presented as amount released after 5 minutes (Q5) and percentage dissolution efficiency (DE).

Formula	Ratios		Q5 (%)	DE (%)
	Cilostazol	Sucralose/Mannitol		
Pure cilostazol	1	0	30.5 ± 1.5	57.5 ± 1.4
Processed cilostazol	1	0	36.7 ± 0.57	57.1 ± 0.7
CS1	1 (1)	1 (1.092)	73.4 ± 1.4	82.5 ± 0.7
CS 2	1 (1)	2 (2.184)	74.4 ± 3.9	82.2 ± 1.4
CS 3	1 (1)	3 (3.186)	78.6 ± 1.5	84.0 ± 0.4
CS4	2 (1)	1 (0.553)	-	-
CS5	3 (1)	1 (0.364)	-	-
CM1	1 (1)	1 (0.493)	52.7 ± 0.57	71.3 ± 1.9
CM2	1 (1)	2 (0.986)	71.3 ± 1.9	80.1 ± 1.5
CM3	1 (1)	3 (1.479)	79 ± 2.7	84.5 ± 1.1

-Values between brackets are the weight ratio in grams

pan which was capped with the lid and loaded onto the furnace together with an empty pan to serve as reference. Thermal analysis was conducted by heating the samples from 30 to 400 °C at a rate of 10 °C. This was conducted under continuous flow of nitrogen gas (20 ml/min). Data collection and analysis was achieved using Pyris software.

Powder X-ray Diffraction (PXRD)

The X-ray diffraction pattern was monitored before and after processing or co-processing using GNR APD 2000 X-ray diffraction system (Agrate, Conturbia, Italy). This equipment has super-speed VA° NTEC-1 detector together with a primary Gobel mirror. The diffraction pattern was recorded at ambient temperature starting from 2 theta of 3 to 50° using scanning step size of 0.03°.

Scanning electron microscopy (SEM)

The morphology of pure cilostazol, sucralose and mannitol and selected formulations were recorded using scanning electron microscope (JSM-5300, Jeol, Tokyo, Japan). The samples were loaded onto the mounting stubs and coated with a thin film of gold using sputter coater (JFC - 1100E), then the SEM was operated between 20 and 25 KeV.

Dissolution studies

Dissolution studies employed the USP paddle type dissolution equipment (Copley Scientific Dis 6000, Nottingham, UK). Cilostazol (100 mg of pure drug or its equivalent from the processed mixtures or tablets) was added to dissolution vessels containing 900 ml of the dissolution media recommended by FDA for cilostazol (0.3% w/v sodium lauryl sulphate in distilled water). The dissolution medium was maintained at 37 ± 1 °C with the paddle rotating at 75 rpm. Dissolution samples (5 ml) were collected 5, 10, 15, 30, 45 and 60 minutes after loading. The samples were immediately filtered, and the dissolution medium was replenished with equal volume after each sample. The concentration of the drug in each sample was quantified using UV spectrophotometry at 257 nm. The dissolution profiles were constructed by plotting the cumulative percentage of cilostazol dissolved as a function of time. The percentage of cilostazol liberated

after 5 minutes (Q5) and the dissolution efficiency (DE) were calculated.¹⁴

Preparation of fast disintegrating tablet

Co-processed formulations showing optimum dissolution profiles were formulated into rapidly disintegrating tablets according to the composition presented in Table 2. Physical mixtures of the components of each formula were prepared and used as control. The components were geometrically mixed before direct compression into 500 mg tablets. This employed a single punch (12 mm rounded) tablet machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India). The compression force was optimized to develop tablets with a hardness of 4–5 Kp. This hardness value is desirable for rapidly disintegrating tablets.⁸

Evaluation of fast disintegrating tablets

The prepared tablets were subjected to full quality control scheme. The uniformity of weight was identified according to the USP specification using randomly selected 20 tablets. The weight of each tablet and the average weight of the 20 tablets were determined. The percentage deviation from the mean for each tablet was then calculated. The tablets conform to the specification if not more than 2 tablets deviate by more than 5% provided that no tablet deviate by more than 10%.¹⁵

$$F = \left[\frac{(W_{initial} - W_{final})}{W_{initial}} \right] \times 100 \quad \text{Eq. (1)}$$

The tablet friability was measured using Erweka friability tester (Heusenstamm, Hesse, Germany). This employed 10 tablets, the weight of which was recorded before and after being subjected to 100 revolutions in the friabilator. The friability (F) was calculated using the following equation. The uniformity of content was assessed by selection of 30 tablets, 10 of which were subjected to drug content measurement. Each tablet was crushed and solubilized in ethanol. The clear solution was separated by centrifugation and suitably diluted before determination of the drug concentration. “The tablets were considered acceptable if the content of each of at least 9 tablets were in the range of 85–115% of the labeled amount of cilostazol. The tenth

Table 2. Composition of the prepared fast disintegrating tablets, along with dissolution parameters illustrated as amount released after 5 minutes (Q5) and percentage dissolution efficiency (DE).

		Unprocessed cilostazol (mg)	Sugar (mg)	Formulation (mg)	CS (mg)	CP (mg)	ME (mg)	Avecil (mg)	Q5	DE (%)
Sucralose	Control tablet	100	109.2	-	25	25	5	235.8	29 (3.7)	59 (0.76)
	CS tablet	-	-	209.2	25	25	5	235.8	72.5 (1.38)	80.4 (0.8)
Mannitol	Control tablet	100	148	-	25	25	5	197	25 (0.5)	48.3 (1.4)
	CM tablet	-	-	248	25	25	5	197	68.3 (4.5)	74.8 (1.7)

ME: Magnesium stearate, CP: Crospovidone, CS: Sodium croscarmellose

tablet should not contain 75% or 125% of the labeled content. If these conditions were not met, the remaining 20 tablets must be analyzed individually and all of them should be within the limit^{2,15}

Fast disintegration was ensured by determination of the disintegration time which utilized 6 tablets using tablet disintegration tester (Erweka, Heusenstamm, Germany) with distilled water being employed as a medium. The time required for disintegration of the 6 tablets was recorded. The wetting time of the tablets was determined according to the established method.^{7,16} This utilized Petri dish which was loaded with circular filter paper and 6 ml of distilled water. Allura red powder was carefully sprinkled over the tablet surface before mounting on wet filter paper. The time required for the red color to appear on the tablet surface was taken as the wetting time.

Statistical analysis

This utilized SPSS 16 and used Kruskal-Wallis test with Tukey's multiple comparison being considered as post hoc test to compare between groups.

Results and Discussion

Fourier-transform infrared (FT-IR) spectroscopy

The structural features of cilostazol were identified using FTIR before and after processing. The FTIR spectra of cilostazol, excipients and their formulations are shown in Figure 1. Pure untreated cilostazol produced a spectrum corresponding to its functional groups. The amide NH

stretching was detected as broad band at 3450 – 3200 cm^{-1} with the amide C=O stretching being seen at 1668 cm^{-1} . The aromatic ring stretching was detected at 1504 cm^{-1} and C-H stretching of the aromatic ring at 3058 cm^{-1} and 3184 cm^{-1} . The vibrations of tetrazole ring skeleton were noticed at 1398 and 1274 cm^{-1} . The absorption band at 1297 cm^{-1} was assigned for –N=N=N- stretching. Aromatic ether stretching was recorded at 1245 cm^{-1} . This spectral pattern agrees with the published spectrum for cilostazol.^{17,18} Wet grinding of cilostazol with ethanol (positive control) showed no change in the spectrum.

The FTIR spectrum of sucralose revealed two absorption bands at 3462 cm^{-1} and 3322 cm^{-1} which can be attributed to free and bonded OH stretching vibration. The strong bands at 1303, 1245, 1139, 1096 and 1037 cm^{-1} can be assigned to the C–O stretching modes. This spectrum is similar to the previously reported for sucralose.⁶ The FTIR spectrum of sucralose did not show any significant changes after co-grinding with ethanol (Figure 1). FTIR spectrum of mannitol showed broad stretching of bonded OH groups at 3402 cm^{-1} and 1284 cm^{-1} represents OH in plane bending, C-O groups stretching of 1ry and 2ry alcohols at 1084 and 1019 cm^{-1} . 2948 cm^{-1} and 2905 cm^{-1} represent CH_2 and CH stretching respectively, at 1423 cm^{-1} CH_2 bending.¹⁹

Co-processing of cilostazol with either sucralose or mannitol produced FTIR spectra which is the summation of the spectral pattern of the components of each mixture. This reflects the absence of significant chemical interaction between cilostazol and sucralose or mannitol.

Differential scanning calorimetry (DSC)

The thermal pattern of cilostazol, sucralose, mannitol was monitored before and after processing or co-processing. The collected thermograms are shown in (Figure 2). These thermograms were used to calculate the thermal parameters which are summarized in Table 3. The unprocessed cilostazol showed thermal behavior of typical crystalline material with a sharp endothermic peak at 160°C corresponding to its melting transition. The thermogram also revealed broad exotherm at 374.7°C corresponding to the decomposition of cilostazol (Figure 2, Table 3). This thermal behavior is similar to that published by other authors.^{5,17} Wet grinding of cilostazol with ethanol (positive control) produced dry product with identical thermal behavior to the unprocessed drug. This suggests that any changes after co-processing with excipient will result from interaction. It is important to highlight that heating and cooling of cilostazol is believed to result in polymorphic transition, with three different polymorphs have been identified.²⁰ The absence of change in the thermal pattern of cilostazol after wet grinding with ethanol indicates that wet grinding in absence of additives did not affect the crystalline structure of the drug.

The thermal behavior of unprocessed sucralose was characterized by its sharp endotherm at 125.5°C with a weak exothermic decomposition at 217°C. Ethanol assisted wet grinding modulated the thermal pattern

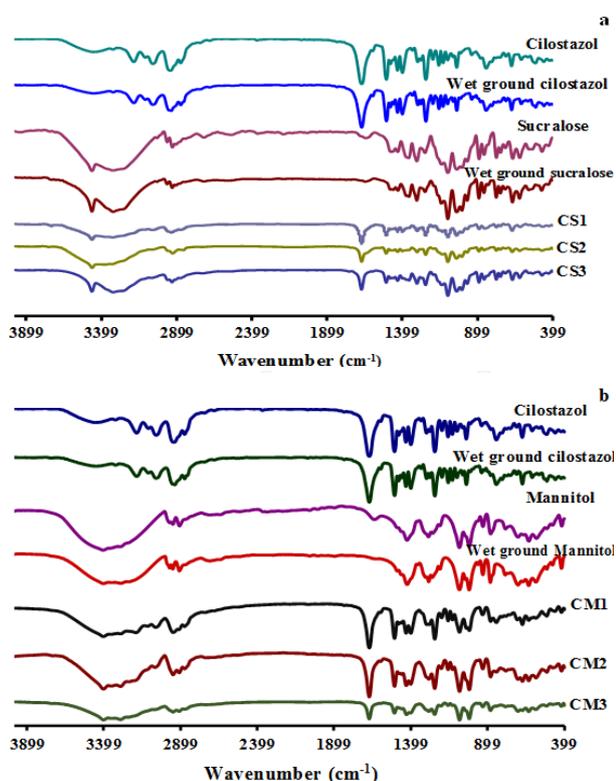


Figure 1. FTIR spectra of processed and unprocessed cilostazol together with different formulations prepared using sucralose (a) and mannitol (b). Formulation details are in Table 1.

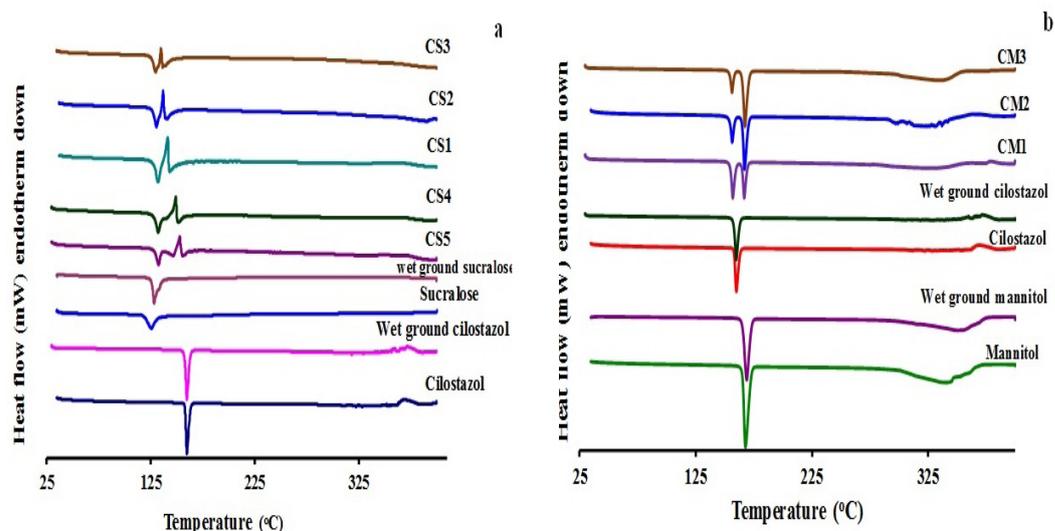


Figure 2. DSC thermograms of processed and unprocessed cilostazol together with different formulations prepared using sucralose (a) and mannitol (b). Formulation details are in Table 1.

Table 3. The parameters calculated for the main endothermic peaks of the pure cilostazol, Sucralose, mannitol, positive controls and the prepared formulations.

Sucralose										
Formula		UP-drug	P-drug	UP-sucralose	P-sucralose	CS1	CS2	CS3	CS4	CS5
1st Endotherm	Onset (°C)	157.9	157.4	118.3	125.9	127	126	125.3	126.4	127
	Endset (°C)	162.8	162.6	131.6	132.2	140.2	37.7	133.9	137.8	140
	Tm (°C)	160	159.8	125.5	128.3	132.1	130.6	129.7	132.5	132
Exotherm	Onset (°C)					138.3	135.3	133.6	147	149.8
	Endset (°C)					142.7	140.6	138	150.2	155
	Tm (°C)					142	137.2	135.5	149.5	153.7
2nd Endotherm	Onset (°C)					143.8	140.6	138	152.8	158
	Endset (°C)					150	148.5	146.8	160	163
	Tm (°C)					144.5	141.4	138.3	154	159
Decomposition	Onset (°C)	363.6	366	200	203	339.7	366.7	375.7	348	360
	Endset (°C)	387.4	388.7	228	230	381	394.3	399	383	388
	Tm (°C)	374.7	374	217	221	365	390.3	391	371	372.2
Mannitol										
Formula		UP-drug	P-drug	UP-mannitol	P-mannitol	CM1	CM2	CM3		
1st Endotherm	Onset (°C)	157.9	157.4	164.9	165	154.5	154	153.9		
	Endset (°C)	162.8	162.6	172	172.4	159.2	158.5	158.1		
	Tm (°C)	159.9	159.8	167.7	168.8	156.7	156.2	156.1		
2nd Endotherm	Onset (°C)					164.6	164.6	164.6		
	Endset (°C)					169	170	170.4		
	Tm (°C)					166.6	166.9	167.2		
Decomposition	Onset (°C)	363.6	366	305.9	373	290.6	291	299.2		
	Endset (°C)	387.4	388.7	349	328	349.1	345	352		
	Tm (°C)	374.4	374	341.3	350.4	332.4	330.5	335.7		

UP: Unprocessed, P: Processed

with the melting transition being seen at 128.3°C and the decomposition exotherm starting at 221°C (Figure 2a). Similar behavior was recorded in the literature with wet processing with other solvents, such as acetone, produced similar changes.⁶

For mannitol, the melting endotherm was revealed at 167.7°C and the sugar decomposed showing broad endotherm at 341.3°C. The recorded thermogram of unprocessed mannitol correlates with the published work on the same sugar.²¹ Wet processing with ethanol increased melting transition to reach 168.8°C and the decomposition to 350.4°C (Table 3 and Figure 2b).

Wet co-grinding of cilstazol with sucralose produced crystalline mixture with thermal behavior which is not the sum of that of both materials. The thermal behavior of the developed product was characterized by complex thermal events which included an endothermic peak followed by a strong exotherm and weak endotherm. The transition temperature of the recorded thermal events is between those of sucralose and cilstazol. For further explanation, co-processed formulations CS4 and CS5 were prepared containing increasing amount of the drug (Table 1 and Figure 2a). The T_m values of the thermal event increased by increasing the proportion of cilstazol in the mixture with separation between the main endotherm and the exotherm being clearer. This thermal behavior can be attributed to solid state transition with possible interaction while fusion and melting. It is important to highlight that

the decomposition exotherm of the drug became weak after co-processing (Figure 2a). The developed thermal behavior reflects possible existence of new crystalline product. It may possibly reflect polymorphic transition of the drug *in situ* during heating, but this assumption requires further verification. Polymorphism has been reported for cilstazol upon thermal processing.²⁰

Wet co-grinding of cilstazol with mannitol resulted in reduction of the melting transition of the drug compared to positive control (Figure 2b). This reflects possible eutectic effect. Eutexia has been recorded for nonsteroidal anti-inflammatory drugs after co-grinding with caffeine.²²

Powder X-ray diffraction (PXRD)

The X-ray diffraction pattern was recorded for the unprocessed and processed cilstazol, sucralose, mannitol and their co-processed products. Representative diffractograms are shown in Figure 3 and the main diffraction peaks are summarized in Table 4. The diffractogram of unprocessed cilstazol revealed its crystalline structure as indicated from the recorded diffraction peaks (Figure 3 and Table 4). The recorded data correlate with the published pattern of the same drug.²³ Grinding of cilstazol after ethanol evaporation resulted in no alterations in the diffractogram, except for some minor reduction in the peak intensity. This may indicate reduction of particle size. The strong diffraction peaks of unprocessed sucralose reflects its strong crystalline nature (Table 4). This diffractogram is similar to previously recorded for the same sugar.⁷ Wet grinding of sucralose compromised the diffraction pattern compared to the unprocessed material with the reduction of the intensity and disappearance of some peaks. Additionally, new diffraction peaks at 2 theta values of 22.98, 25.86, 28.44, 34.77 and 36.24° was noted. These changes in the diffraction pattern indicate that the crystalline structure of sucralose is affected by the organic solvent used (Figure 3a and Table 4). These changes were also reported by other investigators who treated the sugar in a similar way.^{7,8} Additionally, these modifications in the diffraction pattern coincide with the DSC data that showed increase in the T_m value for the processed sucralose that would suggest formation of new crystalline structure.

The diffractogram of unprocessed mannitol showed its crystalline structure as noted from the recorded diffraction peaks (Figure 3b and Table 4). This diffractogram agrees with that reported by other investigators.²⁴ Wet grinding of mannitol with ethanol changed the diffraction pattern. These changes are in the form of reduction in the intensity of some diffraction peaks and appearance of new peaks at 2 theta values of 16.8, 21.69, 26.6, 34.3 and 36.0°. These changes were previously reported for mannitol and was attributed to the effect of the solvent on the crystalline lattice of the material.²⁴ This compromised diffractogram confirms the results of thermal analysis where the decomposition peak of processed mannitol was shifted to higher transition temperature suggesting formation of new crystals of the material.

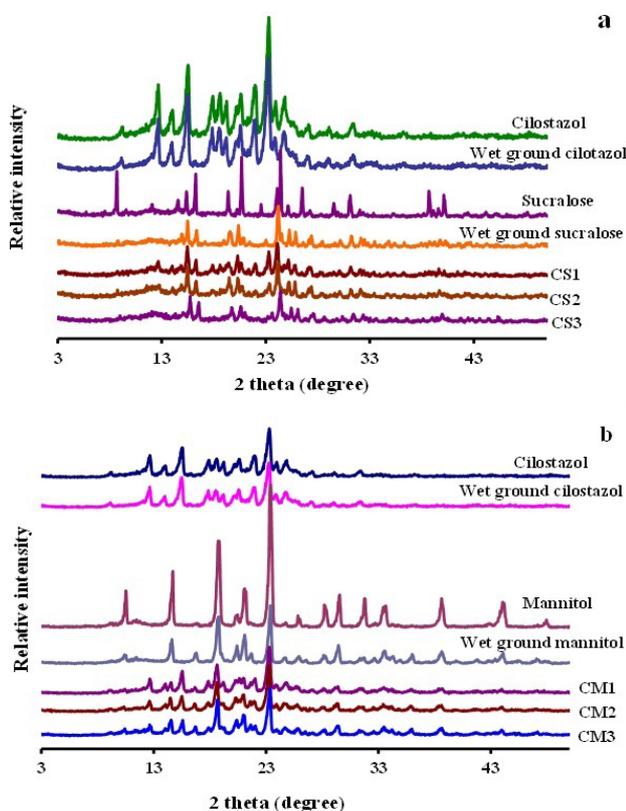


Figure 3. X-ray diffraction of processed and unprocessed cilstazol together with different formulations prepared using sucralose (a) and mannitol (b). Formulation details are in Table 1.

Table 4. The characteristic diffraction peaks of the pure cilostazol, sucralose, mannitol, processed drug, processed mannitol and sucralose together with the prepared formulations.

Formula	2 Theta (degrees)
Pure unprocessed cilostazol	9.24, 12.66, 14.01, 15.5, 17.88, 18.6, 19.23, 20.64, 21.96, 23.28, 23.94, 24.8, 27.18, 29, 31.44, 32.8, 36.24, 38.8
Pure processed cilostazol	9.12, 12.63, 13.98, 15.48, 17.85, 18.5, 19.2, 20.58, 21.84, 23, 23.25, 23.1, 24.8, 27, 29, 31.44, 33.12, 36.2, 41.37
sucralose	8.7, 14.55, 16.26, 19.4, 20.67, 24.42, 26.46, 38.7, 40.2
Wet ground sucralose	8.76, 15.39, 15.48, 16.35, 19.56, 22.98, 25.86, 28.44, 34.77, 36.24, 40.26, 41.4
CS1	12.66, 15.48, 16.26, 20.4, 24.15, 25.28, 27.39
CS2	8.73, 11.52, 12.72, 15.48, 16.26, 19.47, 25.23, 23.34, 27.24
CS3	8.97, 14.3, 15.55, 16.45, 20.4, 24.15, 25.28, 27.5
Pure unprocessed Mannitol	10.5, 14.7, 21.18, 23.37, 28.35, 29.55, 31.74
Wet ground mannitol	10.53, 11.49, 14.61, 16.8, 21.69, 26.6, 34.3, 36
CM1	12.63, 14.04, 14.55, 15.45, 16.77, 18.66, 21.93, 23.31
CM2	10.41, 12.8, 15.5, 16.77, 18.65, 21.93, 23.21
CM3	10.44, 12.5, 15.55, 16.8, 18.5, 21.93, 23.5

Ethanol assisted co-grinding of cilostazol with sucralose produced crystalline products with X-ray diffraction pattern in which the principle peaks of the drugs are either of lower intensity or disappeared. Meantime, the diffractograms showed new diffraction peaks which were of very low intensity. Such pattern fails to confirm the recorded DSC changes which suggest the development

of new crystalline structure but suggest at least a decrease in the crystallinity of the drug after co-processing with sucralose (Figure 3a).

Wet co-grinding of cilostazol with mannitol produced crystalline products which exhibited a diffraction pattern showing the summation of diffraction peaks of the components of each mixture but with low intensity

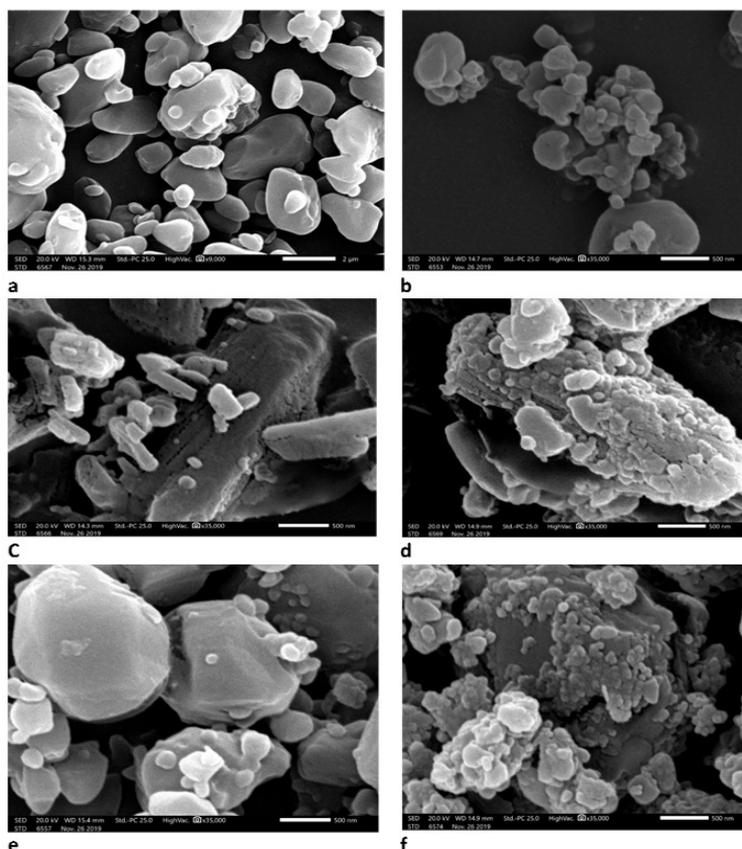


Figure 4. Photomicrographs of unprocessed cilostazol (a), wet ground cilostazol (b), wet ground mannitol (c), a mixture of wet co-ground cilostazol and mannitol at molar ratio 1:2 (d), wet ground sucralose (e), a mixture of wet co-ground cilostazol and sucralose at molar ratio 1:1 (f).

and broader peaks (Figure 3b). Such behavior suggests reduction in the crystallinity with reduced particle size. Absence of significant new diffraction peaks correlates with the thermal analysis results which reflected possible eutectic interaction. Eutexia has been identified with the eutectic products showing no significant change in the diffraction pattern.²²

Scanning Electron Microscope (SEM)

The particle surface morphology and size of the pure cilostazol and its positive control (wet ground cilostazol), wet ground mannitol and sucralose together with selected formulations (CS1 and CM3) were monitored using SEM. The obtained images are shown in Figure 4. The photomicrograph of unprocessed cilostazol showed irregular crystals, mainly prismatic in shape, with good correlation to published SEM of same drug.¹⁷ The mean particle size of cilostazol ranged from 2.5 to 5.0 μm (Figure 4a). For positive control (wet ground cilostazol), it showed significant reduction in size with particle aggregation (Figure 4b). Processed mannitol photomicrograph showed particles of rectangular shape with average particle size of 4 μm . (Figure 4c). The surface morphology also showed high degree of surface porosity. This photomicrograph is in good agreement with published data.¹⁹

The morphology of processed sucralose particles showed irregular shape with flat surface and an average size of about 3 μm , with smaller particles attached to the surface of the bigger particles (Figure 4e).

Wet co-grinding of cilostazol with mannitol produced crystalline products in which mannitol retains its rectangular shape and size, where the drug crystals were markedly reduced in size and deposited over the surface of mannitol particles in a submicron dimension (Figure 4d). Similar findings were also observed for cilostazol/sucralose mixture where small drug crystals were deposited over the sucralose particles (Figure 4f). Similar findings were obtained when wet co-ground mixture of fenofibrate and niacin was prepared.²²

In vitro drug dissolution studies

Dissolution studies were conducted to monitor the effect of co-processing of cilostazol with either sucralose or mannitol on the dissolution pattern. Figure 5 shows the recorded dissolution profiles. The computed dissolution parameters taken as percentage amount released after 5 minutes (Q5) and dissolution efficiency (DE) are presented in Table 1. The dissolution data indicated the slow dissolution pattern of unprocessed cilostazol which liberated a maximum of 30.5% in the first 5 minutes with a total of 82.2% of the dose being liberated after 1 hour. This poor dissolution, especially at the early time, was also reflected in the value of the dissolution efficiency that was only 57.5% (Figure 5a, b and Table 1). This *in vitro* release pattern of cilostazol is similar to the published data.²⁵

Ethanol-assisted grinding of cilostazol in absence of any additive (positive control) slightly increased initial drug

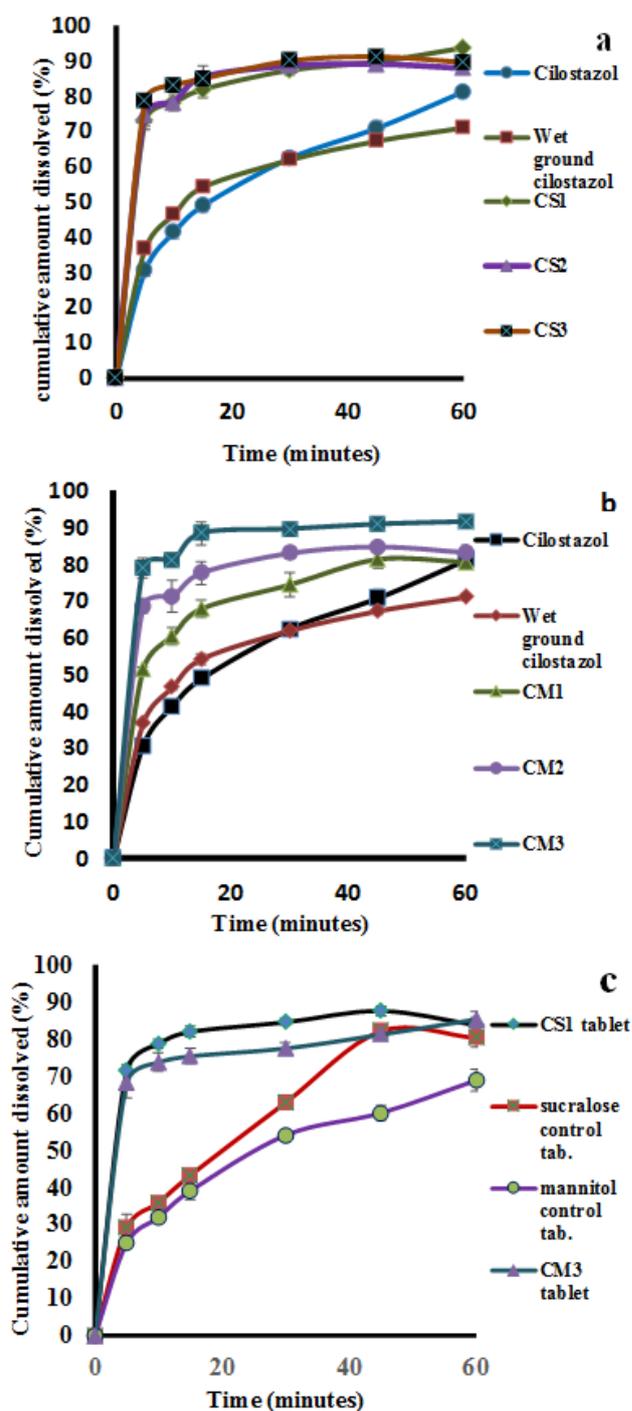


Figure 5. *In vitro* dissolution of cilostazol and formulations with sucralose (a), cilostazol and formulations with mannitol (b) and Fast disintegrating tablets (c). Formulation details are in Tables 1 and 2.

released compared to unprocessed one (Q5 of 36.7%). However, the overall dissolution efficiency was similar ($P > 0.05$).

Wet co-processing of cilostazol with either sucralose or mannitol showed improved dissolution behavior over that of unprocessed or positive control. This was reflected by the enhanced dissolution parameters (Figure 5a, b and Table 1). For co-processed drug with sucralose, formula

CS1(1:1 molar ratio) liberated 73.4% of the loaded dose in the first 5 minutes. The dissolution efficiency increased to 82.5% (Figure 5a and Table 1). The obtained enhancement can be attributed to reduced crystal size due to the adopted technique and the deposition of the drug as fine microcrystals on the surface of sucralose crystals. This supposition can be justified by SEM results. Partial amorphization as per DSC data, is another contributing factor. Increasing sucralose content in formula CS2 (1:2) and CS3 (1:3) slightly increased cilostazol release parameters that was non-significant when compared to that of CS1 ($P > 0.05$). Therefore 1:1 molar ratio was selected as the optimum concentration for this combination.

Co-processing of cilostazol with mannitol improved dissolution behavior (Figure 5b). At equimolar ratio (i.e. formula CM1), there was an initial release of about 52.7% of the drug with dissolution efficiency of 71.3%. Unlike sucralose, drug dissolution increased with increasing mannitol ratio ($p < 0.05$). Formula CM3 (1:3) liberated about 80% of the drug after 5 minutes with total release of more than 90% after 1 hour. The dissolution efficiencies were also increased (Table 1).

The increased drug dissolution with increasing mannitol content can be explained by the proposed eutectic mixture formation. Other reason could be due to the hydrotropic effect of mannitol, as high concentration of the hydrotropic molecules is required for potential dissolution enhancement.²² Mannitol was previously used as hydrotropic agent for enhancing the solubility of nevirapine.²⁶ The suggested eutectic and hydrotropic effect of mannitol can act synergistically with other potential factors mentioned for sucralose to increase drug solubility.

Characterization of fast dissolving tablets

As the majority of patients on cilostazol therapy are elderly patients, it would be beneficial to prepare an easy to use dosage form. Intra-oral tablets, also identified as rapidly disintegrating or rapidly dissolving tablets, have gained a lot of interest in the last decade. This is because it is a suitable way of administering solid dosage form for people with swallowing difficulties and/or geriatric patients. Formulations CS1 and CM3 were selected to prepare fast disintegrating tablets (CS-Tab and CM-Tab, respectively), as they showed the best dissolution parameters. Each tablet contained an amount equivalent to 100 mg of cilostazol from each co-processed product. For comparison, the components of CS1 and CM3 were physically mixed and were used to prepare control tablets and assigned as Sucr-control Tab and Man-control Tab, respectively (Table 2). Tablets were prepared by direct compression method and were subjected to quality tests, the results of which are shown in Table 2.

The results of weight variation test complied with the US Pharmacopeial (USP) requirements for all batches, with a deviation from average weight of less than 1%.¹⁵ The drug content uniformity was in the range of 95–101% indicating that the powder blends were thoroughly mixed with no

flow problems. The recorded friability values were in the range of about 0.5–0.8%. This is acceptable according to USP and indicates satisfactory mechanical strength for handling. All formulations disintegrated within 24 to 30 second.

Wetting time is a specialized test designed for fast disintegrating tablets in order to estimate the time taken for the tablet to disintegrate when placed in a motionless state on the tongue. Its value reflects tablets inner structure and the hydrophilicity of the added excipients. Values of 55 ± 5 , 65 ± 10 , 26 ± 6 and 40 ± 5 second were recorded for Man-control tab, Sucr-control tab, CS-Tab and CM-Tab, respectively. The reduced wetting for tablets containing ethanol assisted co-grinded mixtures could be attributed to the reduced hydrophobicity of the drug crystals obtained after ethanol evaporation in the presence of the hydrophilic sugars.

The dissolution profiles of different tablets are shown in Figure 5c, with dissolution parameters in Table 2. The control tablets containing physical mixture of cilostazol with either mannitol or sucralose showed slow drug dissolution pattern compared to unprocessed drug. The initial release of about 29% and 25% was noted for Sucr-control and Man-control tablets, respectively. The dissolution efficiency of the later was slightly lower than that for the former (Table 2). This may be due to the recorded high compressibility of mannitol.²⁷ Tablets containing co-processed drug with sucralose (CS-Tab) or mannitol (CM-Tab) showed prompt release of cilostazol with Q5 of 72% and 68%, respectively. Regarding the overall dissolution efficiency, both tablets liberated similar amounts of the drug at the end of the dissolution experiment.

Conclusion

Wet co-grinding of cilostazol with either mannitol or sucralose produced a mixture in which the drug is of less crystalline structure and of smaller particle size. The drug crystals deposited in a submicron form over the surface of the sugar particles. The obtained formulations were of better dissolution characteristics relative to the unprocessed drug. This improvement was concentration dependent in case of mannitol. The improved dissolution rate was not affected by compressing the co-processed mixtures into fast disintegrating tablets. The study thus introduced the wet grinding approach with sugar-based excipients as a strategy for the formulation of fast disintegrating tablets for elderly patients with optimum drug release.

Conflict of Interest

The authors claim that there is no conflict of interest.

References

1. Patel SG, Rajput SJ. Enhancement of oral bioavailability of cilostazol by forming its inclusion complexes. *AAPS PharmSciTech*, 2009;10(2):660-9. doi:10.1208/s12249-009-9249-7
2. Jinno J, Kamada N, Miyake M, Yamada K, Mukai T,

- Odomi M, et al. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. *J Control Rel.* 2006; 111(1-2):56-64. doi:[10.1016/j.jconrel.2005.11.013](https://doi.org/10.1016/j.jconrel.2005.11.013)
3. Jinno J, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, et al. In vitro–in vivo correlation for wet-milled tablet of poorly water-soluble cilostazol. *J Control Rel.* 2008;130(1):29-37. doi:[10.1016/j.jconrel.2008.05.013](https://doi.org/10.1016/j.jconrel.2008.05.013)
 4. Bae S. K, Park JB, Seo JH, Choi WK, Park S, Sung YJ, et al. Improved oral absorption of cilostazol via sulfonate salt formation with mesylate and besylate. *Drug Des Dev Ther.* 2015;9:3961-68. doi:[10.2147/DDDT.S87687](https://doi.org/10.2147/DDDT.S87687)
 5. Kim MS, Lee S, Park JS, Woo JS, Hwang SJ. Micronization of cilostazol using supercritical antisolvent (SAS) process: Effect of process parameters. *Powder Tech.* 2007;177(2):64-70. doi:[10.1016/j.powtec.2007.02.029](https://doi.org/10.1016/j.powtec.2007.02.029)
 6. Arafa MF, El-Gizawy SA., Osman MA, EL-Maghraby GM. Cocrystallization for enhanced dissolution rate of nateglinide: In vitro and in vivo evaluation. *J Drug Deliv Sci Tech.* 2017;38:9-17. doi:[10.1080/10837450.2017.1755982](https://doi.org/10.1080/10837450.2017.1755982)
 7. Essa EA, Elbasuony A R, Abdelaziz AE, El Maghraby GM. Co-crystallization for enhanced dissolution rate of bicalutamide: Preparation and evaluation of rapidly disintegrating tablets. *Drug Dev Ind Pharm.* 2019;45(8):1215-23. doi:[10.1080/03639045.2019.1571504](https://doi.org/10.1080/03639045.2019.1571504)
 8. Arafa MF, El-Gizawy SA, Osman MA, El Maghraby GM. Xylitol as a potential co-crystal co-former for enhancing dissolution rate of felodipine: preparation and evaluation of sublingual tablets. *Pharm Deliv Tech.* 2016; 23(5):454-63. doi:[10.1080/10837450.2016.1242625](https://doi.org/10.1080/10837450.2016.1242625)
 9. Das A, Nayak A K, Mohanty B, Panda S. Solubility and dissolution enhancement of etoricoxib by solid dispersion technique using sugar carriers. *ISRN Pharmaceutics.* 2011;2011:819765 doi:[10.5402/2011/819765](https://doi.org/10.5402/2011/819765)
 10. Krishnamoorthy V, Suchandrasen, Prasad VPR. Physicochemical characterization and in vitro dissolution behavior of olanzapine-mannitol solid dispersions. *Braz J Pharm Sci.* 2012;48(2):243-55. doi:[10.5402/2011/819765](https://doi.org/10.5402/2011/819765)
 11. Rodrigues M, Lopes J, Sarraguça M. Vibrational spectroscopy for co-crystals screening. A comparative study. *Molecules.* 2018;23(12):3263-78. doi:[10.3390/molecules23123263](https://doi.org/10.3390/molecules23123263)
 12. Essa EA, Balata GF. Preparation and characterization of domperidone solid dispersion. *Pak J Pharm Sci.* 2012;25(4):783-91.
 13. Essa EA, Elkotb FE, Zin Eldin EE, El Maghraby G. Development and evaluation of glibenclamide floating tablet with optimum release. *Drug Del Sci Tech.* 2015;27:28-36. doi:[10.1016/j.jddst.2015.04.002](https://doi.org/10.1016/j.jddst.2015.04.002)
 14. Khan KA. The concept of dissolution efficiency. *J Pharm Pharmacol.* 1975;27(1):48-9. doi:[10.1111/j.2042-7158.1975.tb09378.x](https://doi.org/10.1111/j.2042-7158.1975.tb09378.x)
 15. United States Pharmacopeia National Formulary 24. Rockville (MD): United States Pharmacopial Convention; 2000.
 16. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. *Int J Pharm PharmSci.* 2009;1(1):219-26.
 17. Desai C, Prabhakar B. Oral disintegrating tablets of cilostazol-HP- β -CD inclusion complex. *Int J Pharm Sci Res.* 2015;6(4):1624-34.
 18. Rychter M, Baranowska-Korczyn A, Milanowski B, Jarek M, Maciejewska BM, Coy EL, et al. Cilostazol-loaded poly(ϵ -caprolactone) electrospun drug delivery system for cardiovascular applications. *Pharm Res.* 2018;35(2):32. doi:[10.1007/s11095-017-2314-0](https://doi.org/10.1007/s11095-017-2314-0)
 19. Bruni G, Berbenni V, Milanese C, Girella A, Cofrancesco P, Bellazzi G, et al. Physico chemical characterization of anhydrous D-mannitol. *J Therm Anal Calorim.* 2009;95(3): 871-6. doi:[10.1021/acs.jpca.6b05244](https://doi.org/10.1021/acs.jpca.6b05244)
 20. Stowell GW, Behme RJ, Denton SM, Pfeiffer I, Sancilio FD, Whittall LB, et al. Thermally prepared polymorphic forms of cilostazol. *J Pharm Sci.* 2002;91(12):2481-8. doi:[10.1002/jps.10240](https://doi.org/10.1002/jps.10240)
 21. Gil A, Barreneche C, Moreno P, Solé C, Inés Fernández A, Cabeza LF. Thermal behaviour of d-mannitol when used as PCM: Comparison of results obtained by DSC and in a thermal energy storage unit at pilot plant scale. *Appl Energy.* 2013; 111:1107-13. doi:[10.1016/j.apenergy.2013.04.081](https://doi.org/10.1016/j.apenergy.2013.04.081)
 22. Alshaikh RA, Essa EA, El Maghraby GM. Preparation of stabilized submicron fenofibrate crystals on niacin as a hydrophilic hydrotropic carrier. *Pharm Dev Tech.* 2020;25 (2):168-77. doi:[10.1080/10837450.2019.1682609](https://doi.org/10.1080/10837450.2019.1682609)
 23. Wang Y, Sun L, Jiang T, Zhang J, Zhang C, Sun C, et al. The investigation of MCM-48-type and MCM-41-type mesoporous silica as oral solid dispersion carriers for water insoluble cilostazol. *Drug Dev Ind Pharm.* 2013;40(6):819-28. doi:[10.3109/03639045.2013.788013](https://doi.org/10.3109/03639045.2013.788013)
 24. Naeem D, Osman M, El Maghraby G, Essa E. Salt and non-salt forming excipients to improve the dissolution of dexibuprofen; formulation of chewable tablets. *European J Biomed Pharm Sci.* 2020;7(1):1-11.
 25. Park JH, Choi HK. Enhancement of solubility and dissolution of cilostazol by solid dispersion technique. *Arch Pharm Res.* 2015;38(7):1336-44. doi:[10.1007/s12272-014-0547-6](https://doi.org/10.1007/s12272-014-0547-6)
 26. Madan JR, Kamate VJ, Dua K, Awasthi R. Improving the solubility of nevirapine using a hydrotrophy and mixed hydrotrophy based solid dispersion approach. *Polim Med.* 2017;47(2):83-90. doi:[10.17219/pim/77093](https://doi.org/10.17219/pim/77093)
 27. Ohrem H L, Schornick E, Kalivoda A, Ognibene R. Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? *Pharm Dev Tech.* 2013;19(3):257-62. doi:[10.3109/10837450.2013.775154](https://doi.org/10.3109/10837450.2013.775154)